COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

Regarding the "expert appraisal for recommending occupational exposure limits for chemical agents"

Assessment of health effects and methods for the measurement of exposure levels in workplace atmospheres for cadmium and its compounds

This document summarises the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee) and the Working Group on metrology.

This summary is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text of March 2016 shall prevail.

Presentation of the issue

On 12 June 2007, AFSSET, which became ANSES in July 2010, was requested by the Directorate General for Labour to conduct the expert appraisal work required for setting occupational exposure limit values (OELVs) for cadmium and its compounds.

France currently has a mean eight-hour exposure value for cadmium and its compounds of 0.05 $mg.m^{-3}$. This value was set in a Circular[1] of the Ministry of Labour (not published in the Official Journal). Note that this circular also sets an indicative 15-minute exposure limit of 0.05 $mg.m^{-3}$ for cadmium oxide (for cadmium) but no 8h-TWA.

The Directorate General for Labour requested ANSES to re-assess this value and, if necessary, propose new occupational exposure limits based on health considerations for cadmium and its compounds.

Scientific background

The French system for establishing OELVs has three clearly distinct phases:

- Independent scientific expertise (the only phase entrusted to ANSES);
- Proposal by the Ministry of Labour of a draft regulation for the establishment of limit values, which may be binding or indicative;
- Stakeholder consultation during the presentation of the draft regulation to the French Steering Committee on Working Conditions (COCT). The aim of this phase is to discuss the effectiveness of the limit values and if necessary to determine a possible implementation timetable, depending on any technical and economic feasibility problems.

[1] Circular of 7 July 1992 amending and supplementing the Circular of 19 July 1982 as amended, on the acceptable values for concentrations of certain hazardous substances in workplace atmospheres

The organisation of the scientific expertise phase required for the establishment of Occupational Exposure Limits (OELVs) was entrusted to AFSSET in the framework of the 2005-2009 Occupational Health Plan (PST) and then to ANSES after AFSSET and AFSSA merged in 2010.

The OELs, as proposed by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee), are concentration levels of pollutants in workplace atmospheres that should not be exceeded over a determined reference period and below which the risk of impaired health is negligible. Although reversible physiological changes are sometimes tolerated, no organic or functional damage of an irreversible or prolonged nature is accepted at this level of exposure for the large majority of workers. These concentration levels are determined by considering that the exposed population (the workers) is one that excludes both children and the elderly.

These concentration levels are determined by the OEL Committee experts based on information available from epidemiological, clinical, animal toxicology studies, etc. Identifying concentrations that are safe for human health generally requires adjustment factors to be applied to the values identified directly by the studies. These factors take into account a number of uncertainties inherent to the extrapolation process conducted as part of an assessment of the health effects of chemicals on humans.

The Committee recommends the use of three types of values:

- 8-hour occupational exposure limit (8h-OEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over the course of an 8-hour work shift. In the current state of scientific knowledge (toxicology, medicine, epidemiology, etc.), the 8h-OEL is designed to protect workers exposed regularly and for the duration of their working life from the medium- and long-term health effects of the chemical in question;
- Short-term exposure limit (STEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over a 15-minute reference period during the peak of exposure, irrespective of its duration. It aims to protect workers from adverse health effects (immediate or short-term toxic effects such as irritation phenomena) due to peaks of exposure;
- Ceiling value: this is the limit of the concentration of a chemical in the worker's breathing zone that should not be exceeded at any time during the working period. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a very short period of exposure.

These three types of values are expressed:

- either in $mg.m^{-3}$, i.e. in milligrams of chemical per cubic metre of air and in ppm (parts per million), i.e. in cubic centimetres of chemical per cubic metre of air, for gases and vapours;
- or in $mg.m^{-3}$, only for liquid and solid aerosols;
- or in $f.cm^{-3}$, i.e. in fibres per cubic centimetre for fibrous materials.

The 8h-OELV may be exceeded for short periods during the working day provided that:

- the weighted average of values over the entire working day is not exceeded;
- the value of the short term limit value (STEL), when it exists, is not exceeded.

In addition to the OELs, the OEL Committee assesses the need to assign a "skin" notation, when significant penetration through the skin is possible (Anses, 2014). This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to implement appropriate preventive measures (such as wearing protective gloves). Skin

penetration of substances is not taken into account when determining the atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The OEL Committee assesses the need to assign an “ototoxic” notation indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended OELs, to enable preventionists to implement appropriate measures (collective, individual and/or medical) (Anses, 2014).

The OEL Committee also assesses the applicable reference methods for the measurement of exposure levels in the workplace. The quality of these methods and their applicability to the measurement of exposure levels for comparison with an OEL are assessed, particularly with regards to their compliance with the performance requirements in the NF-EN 482 Standard and their level of validation.

Organisation of the expert appraisal

ANSES entrusted examination of this request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). The Agency also mandated the Working Group on metrology to assess measurement methods in workplace atmospheres.

The methodological and scientific aspects of the work of this Group were regularly submitted to the Expert Committee.

The report produced by the Working Group takes account of observations and additional information provided by the Committee members.

This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 “Quality in Expertise Activities”.

Preventing risks of conflicts of interest

ANSES analyses interests declared by the experts before they are appointed and throughout their work in order to prevent potential conflicts of interest in relation to the points addressed in expert appraisals.

The experts’ declarations of interests are made public on ANSES's website (www.anses.fr).

Description of the method

For the assessment of the health effects:

A summary report on the health effects of cadmium was prepared by ANSES's officers and submitted to the OEL Committee, which commented on it and added to it.

The summary report was based on bibliographic information taking into account the scientific literature that had been published on this substance up to 2013. The literature search was undertaken in the following databases: Medline, Toxline, HSDB, ToxNet (CCRIS, GENE-TOX, IRIS), ScienceDirect. The source articles cited as references were reassessed when requested by the OEL Committee.

For the assessment of methods for measuring exposure levels in workplace atmospheres:

A summary report was prepared by the Working Group on metrology and submitted to the OEL Committee, which added its own comments.

The summary report presents the various protocols for measuring cadmium and its compounds in workplace atmospheres grouped together based on the methods they use. These methods were then assessed and classified based on the performance requirements set out particularly in the French Standard NF EN 482: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents" and the decision-making criteria listed in the methodology report (Anses, 2014).

A list of the main sources consulted is detailed in the methodology report (Anses, 2014).

These methods were classified as follows:

- Category 1A: the method has been recognized and validated (all of the performance criteria in the NF-EN 482 Standard are met);
- Category 1B: the method has been partially validated (the essential performance criteria in the NF-EN 482 Standard are met);
- Category 2: the method is indicative (essential criteria for validation are not clear enough);
- Category 3: the method is not recommended (essential criteria for validation are lacking or inappropriate).

A detailed comparative study of the methods in Categories 1A, 1B and 2 was conducted with respect to their various validation data and technical feasibility, in order to recommend the most suitable method(s) for measuring concentrations for comparison with OELs.

The collective expert appraisal work and its conclusions and recommendations were adopted on 12 December 2013 by the OEL Committee.

The collective expert appraisal work and the summary report were submitted to public consultation from 12/03/2015 to 12/06/2015. The people or organizations who contributed to the public consultation are listed in appendix of the report (only available in French). The comments received were reviewed by the OEL Committee who adopted this version on 07/03/2016.

Results of the collective expert appraisal on the health effects

Toxicokinetics

Inhalation is the main route of exposure to cadmium (dust, smoke) in workers. In humans, the rate of pulmonary absorption ranges from 40% to 60% and depends on the physico-chemical properties of the compound (Prozialeck and Edwards, 2010). Cadmium can also enter the body by ingestion, and absorption by this route is not negligible (5% of the amount ingested). Conversely, percutaneous absorption of cadmium is not significant (around 0.5%) and has only been observed when the substance has been in contact with the skin for several hours.

Cadmium is distributed around the body by blood circulation. Cadmium is eliminated from blood with a half-life of about 80 to 100 days. In the body, cadmium binds to albumin, erythrocytes or metallothionein (MT) before being distributed to the tissues. Cadmium accumulates mainly in the kidneys (30% of the cadmium body burden) and liver, and to a lesser extent in the bones, muscles and skin. Because of its long half-lives (4 to 19 years in the liver and 10 to 20 years in the kidneys), the body burden of cadmium increases gradually with age. It is also released very slowly, resulting

in significant blood concentrations long after exposure has ceased. Despite this, very few field studies have been conducted to describe the elimination kinetics of blood cadmium after cessation of exposure.

In the kidneys, because of the small size of the cadmium-MT complex, the cadmium may be effectively reabsorbed from the glomeruli into the renal tubules. As it is absorbed, cadmium continues to accumulate (in non-toxic form) in the kidneys until renal MT is saturated (OEHHA, 2006).

In the absence of kidney damage, the cadmium excreted by the kidneys is only a small portion of the total amount of cadmium accumulated in the body. The cadmium that is filtered by the glomerulus is almost entirely reabsorbed by the proximal tubule epithelial cells; little or no cadmium is then excreted in the urine and its half-life may be between 10 and 20 years, or even 40 years according to some authors. Less than 1% of cadmium is excreted in the faeces.

General toxicity

Toxicity in humans

Impairment (reversible or not) in pulmonary function has been observed with single acute exposure to high atmospheric concentrations (above 5 $mg.m^{-3}$) of cadmium (inflammation of the broncho-pulmonary tract, necrosis of lung epithelial cells and pulmonary oedema). Less intense exposure repeated over time could also cause the same effects, but no atmospheric concentrations could be identified. The report of the ASTDR[2] (2012) mentions a phenomenon of tolerance to broncho-pulmonary irritation caused by repeated cadmium exposure.

Most of the studies in the scientific literature report respiratory and/or renal effects for cadmium. Indeed, the lungs and kidneys are the two target organs for which there are robust, quantitative data on exposure by inhalation to cadmium in the workplace.

Field studies show changes in respiratory function in workers exposed to cadmium. The results of these studies show that the observed effects are fairly dependent on exposure levels. Jakubowsky *et al.* (2004) showed a significant decrease in maximum expiratory flow at 50% of forced vital capacity (MEF50) in workers whose cumulative exposure index (CEI) was greater than 4000 $\mu g.m^{-3}$.years (which corresponds to an exposure level of 100 $\mu g.m^{-3}$ for 40 years) compared to the group of unexposed workers and a non-significant decrease in forced expiratory volume in one second (FEV1) but no decrease in forced vital capacity (FVC) in particular (or in the other investigated parameters). Smith *et al.* (1976) reported a decrease in forced vital capacity in workers exposed to over 200 $\mu g.m^{-3}$ (on average) compared to unexposed workers but did not observe any changes in the other parameters investigated for respiratory function.

Davison *et al.* (1988) reported biological changes consistent with emphysema in workers exposed to cadmium (alloy manufacturing) compared to unexposed workers (significantly lower capture and pulmonary transfer of carbon monoxide for workers whose CEI was respectively less than 400 $\mu g.m^{-3}.year^{-1}$ and between 400 and 1600 $\mu g.m^{-3}.year^{-1}$). They did not show a decrease in forced vital capacity in these workers.

Cortona *et al.* (1992) reported a significant increase in residual volume in workers exposed to cadmium (alloy manufacturing) compared to the group of unexposed workers. This increase was 10% in workers whose CEI exceeded 500 $\mu g.m^{-3}$.years (i.e. 12.5 $\mu g.m^{-3}$ for 40 years of exposure).

[2] Agency for Toxic Substances and Disease Registry

They did not show any changes in the other parameters (FVC, FEV1, carbon monoxide capture and transfer factor).

Several field studies have linked atmospheric concentrations of cadmium (measured individually and/or in ambient air) or cumulative exposure indices and impairment of kidney function. Several field studies give useful results with atmospheric measurements and early markers of tubular cytotoxicity (Table 1).

Table 1: Summary of the results of field studies linking atmospheric concentrations of cadmium or CEIs (all the results reported here are in µg.m^{-3} for 40 years of exposure when describing CEIs) to the results of renal function parameters[3].

Reference	n	Relevance	LOAEL	NOAEL	
Glomerular filtration					
Frieberg (1950)	58	yes/no LOAEL only	3000 to 15000		
Early markers of tubulopathy					
Edling *et al.* (1986)	11	no Small study population	90 to 2000 90 to 200		[β2M]u 300 µg/g creatinine (cr) (34 µg/mmol cr)
Jakubowsky *et al.* (1987)	102	no 15-min ambient air measurements only			[β2M]u 380 µg/g cr [RBP]u 130 µg/g cr
Kjellstrom *et al.* (1977)	240	no low [β2M]u threshold	50		[β2M]u 210 µg/l
Ellis *et al.* (1984)	82	no low [β2M]u threshold	10	2.5	[β2M]u 200 µg/g cr And others
Falck *et al.* (1983)	33	no high [β2M]u threshold	30	11.5	[β2M]u 629 µg/g cr And others
Jarup *et al.* (1988)	440	yes	17	3.3	[β2M]u 310 µg/g cr (35 µg.mmol cr)
Mason *et al.* (1988)	75	no unknown [β2M]u and [RBP]u threshold		12.7 15.9	[β2M]u [RBP]u
Thun *et al.* (1989)	45	no high [β2M]u threshold		20	[β2M]u 500 µg/g cr

Even though cadmium accumulates in the liver as it does in the kidneys, which are a target organ for the toxicity of cadmium, the studies undertaken in workers exposed to cadmium did not show harmful effects on the liver. The liver's resistance to the toxic effects of cadmium could be related to the liver's greater capacity to produce metallothioneins, which bind to cadmium and are thus believed to lower concentrations of free cadmium ions (ATSDR, 2012).

Case studies indicate that calcium deficiency, osteoporosis and osteomalacia have developed in workers occupationally exposed over the long term to high levels of cadmium.

However, studies seeking to assess links between cadmium exposure and high blood pressure (which can also be due to renal impairment) have shown conflicting results.

[3] [β2M]u: urinary concentration of beta-2-microglobulin; LOAEL: Lowest Observed Adverse Effect Level; NOAEL: No Observed Adverse Effect Level; [RBP]u: Urinary concentration of retinol-binding protein.

A recent publication by Lei *et al.* (2007) reports pancreatic anomalies observed in populations exposed to cadmium through contaminated food. This study suggests that these anomalies may occur at exposure levels similar to those causing renal impairment. No field studies on exposure by inhalation have investigated this type of effect.

Toxicity in animals

Only a few long-term exposure studies have been undertaken in animals (rats). The lowest LOAEL is 0.0134 $mg.m^{-3}$ for the appearance of adenomatous hyperplasia in the broncho-alveolar region due to exposure to cadmium chloride ($CdCl_2$) for 18 months, 23 hours/day, 7 days/week (Takenaka *et al.*, 1983).

In addition to respiratory effects, studies on exposure through repeated inhalation of Cd in animals have shown the following systemic effects (ATSDR, 2012):

- decreases in body weight, with for intermediate exposure to $CdCl_2$, a NOAEL of 0.394 $mg.m^{-3}$ in female rats and 0.0508 $mg.m^{-3}$ in male rats;
- hepatic effects: increase in serum levels of alanine aminotransferase, an indicator of liver damage, in rats exposed for 30 days to 0.1 $mg.m^{-3}$ (form not specified), increased liver weight in rats exposed to 1.06 $mg.m^{-3}$ of $CdCl_2$, 6 hours/day for 62 days. In general, the effects observed in the liver, where cadmium nonetheless accumulates, are moderated due to this organ's high capacity to produce metallothioneins;
- renal effects: proteinuria in rabbits exposed for four months to 4 $mg.m^{-3}$ of cadmium metal, for 3 hours/day and 21 days/month, with the appearance of renal lesions when exposure lasted three to four months more;
- immunological effects: spleen weight gain and hyperplasia of the lymphoid tissues in rats exposed to 1.06 $mg.m^{-3}$ of $CdCl_2$, 6 hours/day for 62 days, and in gestating female rats exposed to 0.394 $mg.m^{-3}$ 24 hours/day during the 21 days of gestation.

It should be noted that the studies dealing with haematological effects gave conflicting results and the only study examining neurological effects did not give any results.

Carcinogenic effects - genotoxicity

The carcinogenic effects of cadmium compounds were re-assessed by the IARC[4] in 2012 (IARC, 2012). The IARC experts concluded that:

- there was sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds (lungs as well as kidneys and prostate), although they pointed out that the epidemiological studies had many limitations;
- there was sufficient evidence in animals for the carcinogenicity of cadmium compounds;
- there was limited evidence in animals for the carcinogenicity of cadmium metal.

Reproductive toxicity

The ATSDR report (2012) indicates that there is little evidence of reproductive toxicity for cadmium. Two studies in the workplace are reported but the exposure measurements did not

[4] International Agency for Research on Cancer

include measurements of atmospheric concentrations (only assays of cadmium in the blood and/or urine).

Establishment of OELs

8h-OEL

Given the results of genotoxicity studies, cadmium is considered as an indirect genotoxic agent (IARC, 1993). Thus, it appears there is a threshold for the carcinogenicity of cadmium.

The most suitable epidemiological study for the establishment of a carcinogenic OEL appears to be that by Thun *el al.*, 1985. In this study, lung cancer mortality significantly increased in workers in a plant using cadmium. A statistically significant dose-response relationship was observed between mortality related to lung cancer and cumulative cadmium exposure. This study dealt with employees in a plant producing cadmium oxide, cadmium sulphide and cadmium metal. Estimated exposure levels were 1.16 $mg.m^{-3}$ before 1950, 0.50 $mg.m^{-3}$ between 1950 and 1959, 0.34 $mg.m^{-3}$ between 1960 and 1964 and 0.26 $mg.m^{-3}$ between 1965 and 1976 (Smith *et al.*, 1980). Several confounding factors were taken into account in the analysis (cigarette smoking, exposure to arsenic).

Recent reviews (ATSDR, 2012; Verougstraete *et al.*, 2003) and new studies (Järup *et al.*, 1998; Sorahan *et al.*, 2004) attribute a share of the observed increase in lung and prostate cancers to smoking and/or exposure to other known carcinogens such as arsenic and nickel. Moreover, in 1993, the IARC had reported field studies showing an increase in lung cancers in workers not exposed to arsenic or nickel (IARC, 1993).

In any case, it does not seem possible to properly assess the dose-response relationship given that co-exposure to other carcinogens cannot be ruled out.

While studies in rats clearly show a carcinogenic effect of cadmium (with no possible confounding factors), extrapolations to humans, particularly for the establishment of OELs, do not seem legitimate given the major differences observed between animal species (e.g. rats, mice, hamsters) regarding the carcinogenic effects of cadmium. These differences are due to the capacity for production of metallothioneins, proteins that sequester cadmium.

The OEL Committee indicates that there is sufficient evidence of carcinogenicity for cadmium and its compounds. The OEL Committee also considers that the genotoxic action of cadmium may be indirect and concludes that there is a concentration threshold for its carcinogenicity. However, given the uncertainties mentioned for the identification of a point of departure (or critical dose) based on lung (or prostate) cancer, the OEL Committee decided to establish an 8h-OEL based on another critical effect (pragmatic 8h-OEL).

It is not possible to know whether the proposed pragmatic 8h-OEL could prevent potential carcinogenic effects. Therefore, its main purpose is to limit exposure.

Choice of critical effects

Chronic renal toxicity in workers exposed to cadmium has been established. Most studies do not give results on atmospheric exposure levels for cadmium but describe urine and blood concentrations of cadmium associated with biomarkers of effects.

The precursor to renal toxicity related to cadmium is an increase in low-molecular-weight proteins in urine.

It is acknowledged in the various studies that an increase in urinary concentrations of β2M or RBP above 1,000 µg.g^{-1} creatinine is a marker of irreversible tubular cytotoxicity. It is also acknowledged that urinary concentrations greater than 300 µg.g^{-1} creatinine are a first sign of tubular cytotoxicity that must be prevented (Prozialeck and Edwards, 2010; Hotz *et al.*, 1999; Bernard, 2004; Jarup *et al.*, 1998). That is why a urinary concentration of 300 µg.g^{-1} creatinine for RBP or β2M is often used as a toxicity threshold for cadmium to investigate its tubulotoxic potential.

The OEL Committee therefore decided to choose impairment of renal function as the critical effect to establish the pragmatic 8h-OEL for cadmium and its compounds.

Choice of key study

There are different criteria for defining impairment of renal function in the studies identified in the literature (increase in early markers of tubular cytotoxicity above a threshold that differs from one study to another, or biological measurements that reflect an irreversible disease such as decreased glomerular filtration).

The study by Jarup *et al.* (1988) was chosen as the key study since it has two major advantages over the other studies:

- the threshold concentration of urinary β2M in this study is 310 µg.g^{-1} creatinine. This concentration is generally used as a toxicity threshold for cadmium onrenal function and was also used by the OEL Committee for the establishment of a biological limit value for cadmium in the urine and blood;
- the study included a large number of workers (440) and has been described in several publications specifying the exposure measurements taken to assess exposure levels for the workers included in the study (atmospheric metrology used – sampling in ambient air versus individually –, exposure histories, sampling devices used).

This study has some limitations that should be mentioned:

- for the period prior to 1945, atmospheric concentrations were estimated based on the company's historic data with different sampling systems depending on the period;
- the evaluation of exposure took into account both ambient air sampling and individual sampling;
- the sampled fraction was not always known.

These limitations may result in exposure levels being under-estimated.

Identifying the point of departure

The OEL Committee recommends using the average cumulative exposure index as the NOAEL, as identified in the study by Jarup *et al.* (1988), for the class of workers with a 1% prevalence of exceeding the threshold concentration of [β_2M]u (310 µg.g^{-1} creatinine), i.e. a CEI of 131 µg.m^{-3}.years. The atmospheric concentration extrapolated from this CEI to 40 years of exposure is 3.275 µg.m^{-3}.

Establishment of the 8h-OEL – Application of adjustment factors

The OEL Committee does not consider that it is necessary to apply adjustment factors. Indeed, since the point of departure (POD) was determined based on a study undertaken with a large number of workers over a long period, it does not seem relevant to use an adjustment factor to take into account inter-individual variability. This is also supported by the choice of POD, which relies on a relatively conservative approach by considering the average for the exposure class and not the upper bound.

Therefore, the OEL Committee recommends a pragmatic 8h-OEL of 3 µg.m^{-3}.

In this study, the authors specified that the sampled particles essentially corresponded to the respirable fraction (information reported in the publication by Adamsson, 1979). The 8h-OEL calculated from this study should therefore be measured by sampling the respirable fraction. However, local effects related to particles being deposited in the respiratory tract need to be considered. As a lung carcinogen, an approach that involves applying the same OEL for respirable particles and inhalable fraction can be justified as more protective: therefore, the OEL Committee recommends measuring exposure by sampling the inhalable fraction.

This value is consistent with that recommended by the SCOEL[5] (4 µg.m^{-3} for the respirable fraction), which considered an atmospheric concentration of 12.5 µg.m^{-3} (extrapolated from a CEI of 500 µg.m^{-3}.years for 40 years of exposure) as a LOAEL based on a 10% prevalence of workers showing a decrease in residual volume observed in the study by Cortona *et al.* (1992).

Moreover, the study by Alesio *et al.* (1993), which compared blood concentrations of cadmium (reflecting recent exposure) with atmospheric concentrations, is also worth noting. Indeed, the blood concentration reported in this study, which is the closest to but still lower than the BLV recommended by the OEL Committee (of 4 µg.l^{-1}), corresponds to an atmospheric concentration of 1 to 10 µg.m^{-3}, which is also consistent with the OEL proposed here by the OEL Committee.

15min-STEL

The phenomena of broncho-pulmonary irritation described above could justify limiting the intensity of exposure peaks.

However, based on the available data, it is not possible to determine an atmospheric concentration not to be exceeded to prevent effects on respiratory function caused by exposure peaks. Therefore, the OEL Committee, in accordance with the methodology it adopted (AFSSET, 2009), recommends not exceeding an atmospheric concentration equivalent to 5 times the recommended 8h-OEL, i.e. 15 µg.m^{-3}, over a period of 15 minutes (sampling the inhalable fraction).

[5] Scientific Committee for Occupational Exposure Limits Limits ; SCOEL. 2010. SCOEL/SUM/138 Cadmium and its inorganic compounds. Recommendation from the SCOEL. (Scientific Committee on Occupational Exposure Limits: Luxembourg, France). 26 p.

"Skin" notation

Cadmium is responsible for systemic effects but it was not possible, lacking sufficient data to calculate a skin permeation flow, to perform the ECETOC[6] calculation. However, the study undertaken by Wester *et al.*, 1992 *in vitro* on human skin showed that less than 1% of the labelled dose of cadmium chloride could be absorbed by the skin within 16 hours. It therefore does not seem appropriate to recommend the "skin" notation for cadmium.

"Ototoxic" notation

No data on the ototoxic effects of cadmium with or without co-exposure to noise were identified in the literature. It therefore does not seem appropriate to recommend the "ototoxic" notation for cadmium.

Results of the collective expert appraisal on measurement methods in workplace atmospheres

Assessment of methods for measuring cadmium and its compounds in workplace atmospheres

The following table presents the measurement methods that were identified and evaluated.

No.	Method	Similar protocols[7]
Active sampling with a system for sampling the inhalable or respirable fraction		
1	Analysis by flame atomic absorption spectroscopy (FAAS) **N.B.** The BIA, HSE, ISO and INHST methods use an inhalable dust sampler	INRS MétroPol 003 (2008), NF X 43 257 (2007) + NF X 43-275 (2002), BGI ZH 1/120.54E (1994), HSE MDHS 10-2 (1994), NIOSH 7048 (1994), OSHA ID-189 (1992), [OSHA ID-121 (2002)], IRSST 19-2 (1990), ISO 11174 (1996), INSHT MA-025/A92 (1992)
2	Analysis by electrothermal atomic absorption spectroscopy (graphite furnace) (GF AAS) **N.B.** The BGI, HSE and ISO methods use an inhalable dust sampler	INRS MétroPol 003 (2008), BGI ZH 1/120.54E (1994), HSE MDHS 10/2 (1994), OSHA ID-189 (1992), ISO 11174 (1996)
3	Analysis by plasma emission spectrometry (ICP) **N.B.** The ISO method uses an inhalable dust sampler	INRS MétroPol 003 (2008), INRS MétroPol 113 (2010), ISO 15202 3 sections (2012-2012-2005), OSHA ID-125G (2002), OSHA ID-206 (1991) (soldering), NIOSH 7300, 7301 and 7303 (2003)
4	Analysis by x-ray fluorescence spectroscopy (XRFS)	HSE MDHS-91 (1998)
5	Analysis by plasma mass spectrometry (ICP-MS)	OSHA 1006 (2005), ASTM D7439 (2008), ISO 15202 1&2 (2012) + ISO 30011 (2010), IRSST MA-362 (2010), Ashley *et al.* JEM (2012)

[6] European Centre for Ecotoxicology and Toxicology of Chemicals
[7] ASTM: American Society for Testing and Materials, HSE: Health and Safety Executive, IRSST: Institut de recherche Robert-Sauvé en santé et en sécurité du travail, INSHT: Instituto Nacional de Seguridad e Higiene en el Trabajo, INRS: Institut National de Recherche et de Sécurité, MDHS: Methods for the Determination of Hazardous Substances, NIOSH: National Institute for Occupational Safety and Health, OSHA: Occupational Safety and Health Administration.

The following two graphs present the ranges for which the various methods were tested and their limits of quantification in light of the pragmatic 8h-OEL and 15min-STEL recommended by the OEL Committee.

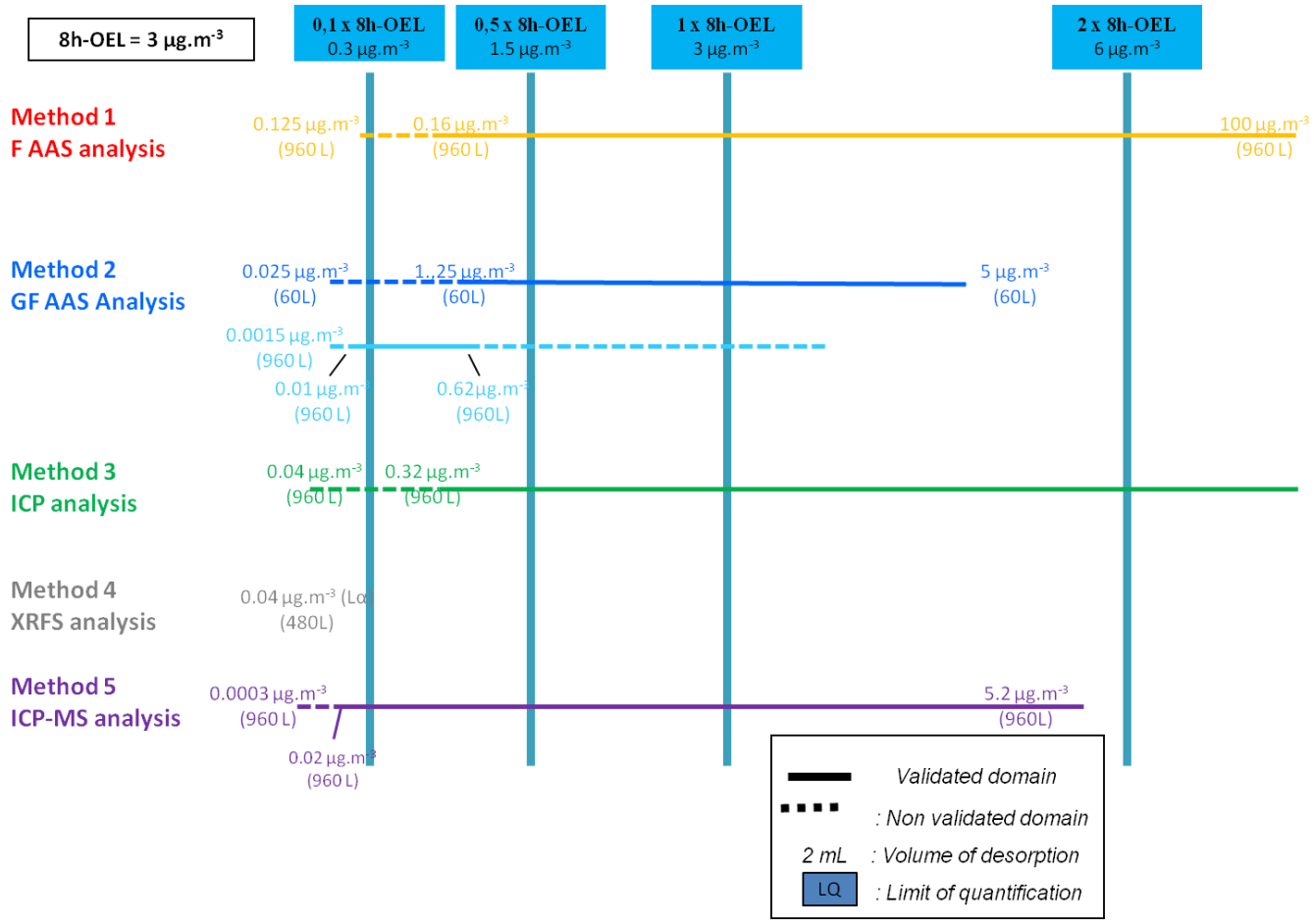

Figure 1: Ranges of validity and limits of quantification for the various compared methods from 0.1 to 2 times the 8h-OEL recommended by the OEL Committee for cadmium and its compounds

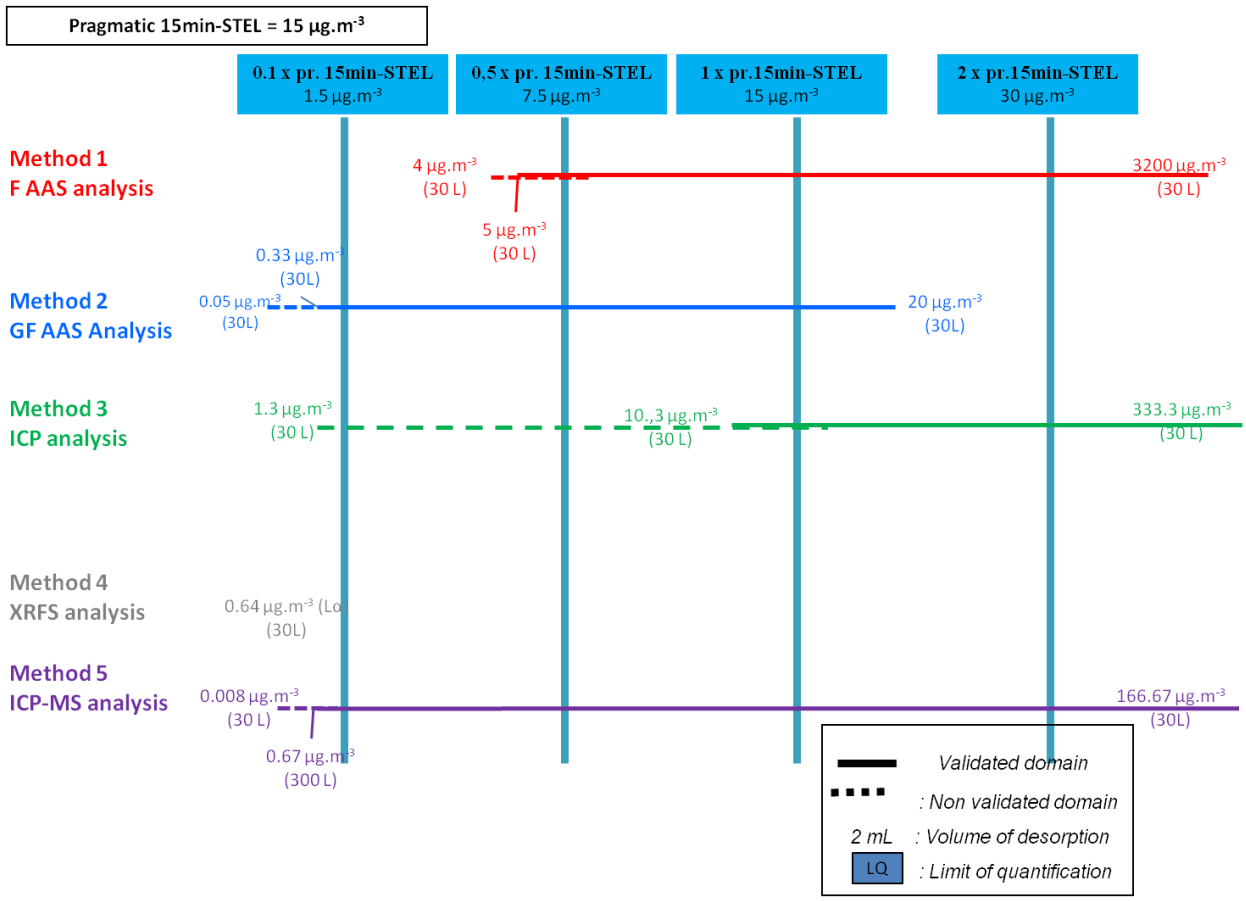

Figure 2: Ranges of validity and limits of quantification for the various compared methods from 0.1 to 2 times the pragmatic 15min-STEL recommended by the OEL Committee for cadmium and its compounds

Conclusion and recommendations

For all of the identified methods, sampling can be performed with a device for sampling the inhalable fraction or respirable fraction. In line with the OEL Committee's recommendation that the inhalable fraction should be considered, a system for sampling the inhalable fraction should be used.

In France, the sampler used is the closed face 37mm-cassette with 4mm inlet at a flowrate of 2 $l.min^{-1}$.

One of the identified methods perfectly meets the requirements of the NF EN 482 Standard to be classified in category 1A. This method is based on the analysis of cadmium and its compounds by ICP-MS. However, the analytical sensitivity (limit of detection) of this technique is highly dependent on the matrix of the sample in the solution, which depends on the sample mineralisation method and sampling medium. Thus, media made of cellulose esters or PVC appear the most suitable for analysis by ICP-MS (lower blank levels). Likewise, the acid load of the solutions before analysis should be reduced as much as possible to guarantee the lowest limits of quantification. If this compromise cannot be reached, two alternative methods classified in category 1B are adaptable for measuring the 8h-OEL of 3 $\mu g.m^{-3}$ recommended by the OEL Committee. These two methods are based on the analysis of cadmium by flame atomic absorption

spectroscopy and inductively coupled plasma atomic emission spectrometry, which are less sensitive to matrix effects than ICP-MS.

For laboratories that do not have this type of equipment, two alternative methods classified in category 1B are adaptable for measuring the pragmatic 8h-OEL of 3 µg.m^{-3} recommended by the OEL Committee. These two methods are based on the analysis of cadmium by flame atomic absorption spectroscopy and inductively coupled plasma atomic emission spectrometry.

The OEL Committee also recommends not exceeding five times the value of the 8h-OEL (i.e. 15 µg.m^{-3}) over a 15-minute period. In this context, the method based on analysis by mass spectrometry remains suitable (1A) and the method based on analysis by emission spectrometry remains partially suitable (1B). The method based on the analysis of cadmium by flame atomic absorption spectroscopy is not sensitive enough but an alternative is possible with an electrothermal atomiser, which is more sensitive and is classified in category 1B for the monitoring and/or regulatory control of a potential pragmatic 15min-STEL.

All of these methods are sensitive and selective and use common laboratory techniques and equipment.

The group of experts therefore recommends the following methods:

- For the regulatory control of the 8h-OEL:

No.	Method	Similar protocols	Category
Active sampling with a system for sampling the inhalable fraction			
1	Analysis by flame atomic absorption spectroscopy (F AAS)	INRS MétroPol 003 (2008), NF X 43 257 (2007) + NF X 43-275 (2002), BGI ZH 1/120.54E (1994), HSE MDHS 10-2 (1994), NIOSH 7048 (1994), OSHA ID-189 (1992), [OSHA ID-121 (2002)], IRSST 19-2 (1990), ISO 11174 (1996), INSHT MA-025/A92 (1992)	**1B**
3	Analysis by plasma emission spectrometry (ICP)	INRS MétroPol 003 (2008), INRS MétroPol 113 (2010), ISO 15202 3 sections (2012-2012-2005), OSHA ID-125G (2002), OSHA ID-206 (1991) (soldering), NIOSH 7300, 7301 and 7303 (2003)	**1B**
5	Analysis by plasma mass spectrometry (ICP-MS)	OSHA 1006 (2005), ASTM D7439 (2008), ISO 15202 1&2 (2012) + ISO 30011 (2010), IRSST MA-362 (2010)	**1A**

- For the monitoring of short-term exposure and for the regulatory control of the pragmatic 15min-STEL:

No.	Method	Similar protocols	Category
Active sampling with a system for sampling the inhalable fraction			
2	Analysis by electrothermal atomic absorption spectroscopy (graphite furnace) (GF AAS)	INRS MétroPol 003 (2008), BGI ZH 1/120.54E (1994), HSE MDHS 10/2 (1994), OSHA ID-189 (1992), ISO 11174 (1996)	**1B**
3	Analysis by plasma emission spectrometry (ICP)	INRS MétroPol 003 (2008), INRS MétroPol 113 (2010), ISO 15202 3 sections (2012-2012-2005), OSHA ID-125G (2002), OSHA ID-206 (1991) (soldering), NIOSH 7300, 7301 and 7303 (2003)	**1B**
5	Analysis by plasma mass spectrometry (ICP-MS)	OSHA 1006 (2005), ASTM D7439 (2008), ISO 15202 1&2 (2012) + ISO 30011 (2010), IRSST MA-362 (2010)	**1A**

Conclusions of the collective expert appraisal

Based on the data currently available, the OEL Committee recommends establishing a pragmatic 8h-OEL of 3 µg.m^{-3} (sampling of the inhalable fraction) for cadmium and its compounds and a pragmatic 15min-STEL of 15 µg.m^{-3} (sampling of the inhalable fraction).

The OEL Committee does not recommend a "skin" notation or "ototoxic" notation.

In light of the assessment of methods for measuring cadmium and its compounds in workplace atmospheres, the OEL Committee recommends the method using active sampling with a system for sampling the inhalable fraction followed by analysis by plasma mass spectrometry. This method has been validated and classified in category 1A for the regulatory control of the 8h-OEL, the monitoring of short-term exposure and the regulatory control of the pragmatic 15min-STEL. The OEL Committee nonetheless notes that this method is sensitive to matrix effects, depending on the sample mineralisation method and sampling medium.

Other alternative analytical methods less sensitive to matrix effects than ICP-MS have been classified in category 1B:

- for the regulatory control of the 8h-OEL:
    - cadmium analysis by flame atomic absorption spectroscopy
    - inductively coupled plasma atomic emission spectrometry
- for the monitoring of short-term exposure and the regulatory control of the pragmatic 15min-STEL[8]:
    - cadmium analysis by electrothermal atomic absorption spectroscopy
    - inductively coupled plasma atomic emission spectrometry

[8] Validation and performance criteria for methods for monitoring STELs are defined in the NF EN 482 Standard from 0.5 to 2 times the STEL. Under the French regulations, for the technical control of the exposure limit, the measurement method must be able to measure one-tenth of the 15min-STEL (Ministerial Order of 15 December 2009 on technical controls of occupational exposure limits in workplace atmospheres and conditions for accrediting the organisations in charge of controls, published in the OJ of 17 December 2009). As such, when a method cannot measure one-tenth of the 15min-STEL, it cannot be classified in category 1A or 1B for regulatory control of the 15min-STEL. However, it may be classified in category 1A or 1B solely for assessing occupational exposure.

References

Afsset. 2009. Recommandations en vue de limiter l'importance et le nombre de pics d'exposition dans une journée de travail (partie 1). (Agence française de sécurité sanitaire de l'environnement et du travail, Maisons-Alfort). 107 p.

Anses. (2014). Reference Document for the derivation and the measurement of exposure limit values for chemical agents in the workplace (OELs). Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, Maisons-Alfort. 115 p.

ATSDR. 2010. Toxicological Profile for Cadmium. (Agency for Toxic Substances and Disease Registry: Atlanta, United States). 319 p.

Adamsson E. 1979. Long-term sampling of airborne cadmium dust in an alkaline battery factory. Scand J Work Environ Health 1979;5(3):178-187.

Bernard, A., 2004. Renal dysfunction induced by cadmium: biomarkers of critical effects. Biometals 17, 519-523.

Cortona G, Apostoli P, Toffoletto F, et al. 1992. Occupational exposure to cadmium and lung function. In: Nordberg GF, Herber RFM, Alessio L, eds. Cadmium in the human environment: Toxicity and carcinogenicity. IARC Scientific Publications No. 118. (International Agency for Research on Cancer: Lyon, France). 205-210.

Davison AG, Fayers PM, Taylor AJ, et al. 1988. Cadmium fume inhalation and emphysema. Lancet 1(8587):663-667.

Edling C, Elinder CG, Randma E. 1986. Lung function in workers using cadmium containing solders. Br J Ind Med. 43(10):657-662.

Ellis KJ, Yuen K, Yasumura S, et al. 1984. Dose-response analysis of cadmium in man: Body burden vs kidney dysfunction. Environ Res 33:216-226.

Falck FY Jr, Fine LJ, Smith RG, et al. 1983. Occupational cadmium exposure and renal status. Am J Ind Med. 4(4):541-9.

Friberg L. 1950. Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning; a clinical and experimental study. Acta Med Scand Suppl. 240:1-124.

Hotz P., Buchet J. P., Bernard A, et al.(1999). Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. Lancet. 354(9189): 1508-1513.

IARC. 2012. Volume 100C: A Review of Human Carcinogens: Arsenic, Metals, Fibres, and Dusts. IARC monographs on the evaluation of carcinogens risks to human. (International Agency for Research on Cancer: Lyon, France). 501 p.

IARC. 1993. Volume 58: Beryllium, cadmium, mercury and exposure in the glass manufacturing industry. IARC monographs on the evaluation of carcinogens risks to human. (International Agency for Research on Cancer: Lyon, France). 453 p.

Jakubowski M, Abramowska-Guzik A, Szymczak W, Trzcinka-Ochocka M. 2004. Influence of long-term occupational exposure to cadmium on lung function tests results. Int J Occup Med Environ Health. 17(3):361-368.

Jakubowski M, Trojanowska B, Kowalska G, et al. 1987. Occupational exposure to cadmium and kidney dysfunction. Int Arch Occup Environ Health 59:567-577.

Jarup L. Berlglund M., Elinder C. G.,et al. 1998. Health effects of cadmium exposure – a review of the literature and risk estimate. Scandinavian Journal of Work and Environmental Health. 24(suppl 1): 1-51.

Järup L, Elinder CG, Spång G. 1988. Cumulative blood-cadmium and tubular proteinuria: a dose-response relationship. Int Arch Occup Environ Health. 60(3):223-229.

Kjellström T, Evrin PE, Rahnster B. 1977. Dose-response analysis of cadmium-induced tubular proteinuria: a study of urinary beta2-microglobulin excretion among workers in a battery factory. Environ Res.13(2):303-317.

Lei LJ, Chen L, Jin TY, Nordberg M, Chang XL. 2007. Estimation of benchmark dose for pancreatic damage in cadmium-exposed smelters. Toxicol Sci. 97(1):189-195.

Mason HJ, Davison AG, Wright AL, et al. 1988. Relations between liver cadmium, cumulative exposure, and renal function in cadmium alloy workers. Br J Ind Med. 45(12):793-802.

OEHHA. 2006. Public heath goals for chemicals in drinking water. Cadmium. December 2006. 82 p.

Prozialeck W. C., Edwards J. R. 2010. Early biomarkers of cadmium exposure and nephrotoxicity. Biometals 23(5): 793-809.

Roels HA, Lauwerys RR, Buchet JP, Bernard A, Chettle DR, Harvey TC et al. 1981. In vivo measurement of liver and kidney cadmium in workers exposed to this metal: its significance with respect to cadmium in blood and urine. Environ Res 26(1):217-40.

SCOEL. 2010. SCOEL/SUM/138 Cadmium and its inorganic compounds. Recommendation from the SCOEL. (Scientific Committee on Occupational Exposure Limits: Luxembourg, France). 26 p.

Smith TJ, Anderson RJ, Reading JC. 1980. Chronic cadmium exposures associated with kidney function effects. Am J Ind Med. 1(3-4):319-37.

Smith TJ, Petty TL, Reading JC, et al. 1976. Pulmonary effects of chronic exposure to airborne cadmium. Am Rev Resp Dis 114:161-169.

Sorahan T, Esmen NA. 2004. Lung cancer mortality in UK nickel-cadmium battery workers, 1947-2000. Occup Environ Med. 2004 Feb;61(2):108-16.

Takenaka S, Oldiges H, Konig H, et al. 1983. Carcinogenicity of cadmium chloride aerosols in W rats. J Nat1 Cancer Inst 70:367-373.

Thun MJ, Osorio AM, Schober S, Hannon WH, Lewis B, Halperin W. 1989. Nephropathy in cadmium workers: assessment of risk from airborne occupational exposure to cadmium. Br J Ind Med. 46(10):689-697.

Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. 1985. Mortality among a cohort of U.S. cadmium production workers - an update. J Natl Cancer Inst. 74(2):325-333.

Verougstraete V, Lison D, Hotz P. 2003. Cadmium, lung and prostate cancer: a systematic review of recent epidemiological data. J Toxicol Environ Health B Crit Rev 6(3): 227-255.

Wester RC, Maibach HI, Sedik L, Melendres J, DiZio S, Wade M (1992). In vitro percutaneous absorption of cadmium from water and soil into human skin. Fundam Appl Toxicol 19(1):1-5.